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Outcomes of a Pharmacist Managed Anticoagulation Service

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Abstract
Objective: Managing patients on warfarin within a therapeutic range is complex due to factors that affect warfarin dosing, making it necessary to monitor patients closely and adjust medication doses to ensure maximal efficacy and minimal adverse events. The objectives of this study were to evaluate the effectiveness and safety of managing patients on warfarin by clinical pharmacists and physicians.
Design: The study was a retrospective chart review.
Setting: This study took place at the Internal Medicine Faculty Associates ambulatory care clinic affiliated with Atlantic Health System, which services patients in northern New Jersey.
Participants: Patients were included in the study if they were seen at the clinic and prescribed warfarinfrom 2012 – 2014. Patients were divided into a pharmacist-managed armand the usual care arm.
Measurements: The primary endpoint wastime in therapeutic range (TTR), calculated based on the Rosendaal method.
Results: A total of 122 patients were included in the final analysis with 53 patients in the pharmacist-managed arm and 69 patients in the usual care arm. The calculated TTR was 66% for the pharmacist-managed arm and 56.6% for the usual care arm ($p = 0.028$). The number of INR tests per patient year was 19.59 in the pharmacist-managed arm compared to 15.04 in the usual care arm ($p = 0.0113$). The percent of patients who had at least one INR > 4 was 28% in the pharmacist-managed arm and 45% in the usual care arm ($p = 0.06$).
Conclusion: Pharmacist-management of warfarin led to a higher average TTR without any differences in supratherapeutic INRs.

I. INTRODUCTION

The framework for the understanding of thrombosis began in mid-1850 with Rudolph Virchow, a German doctor who identified three components contributing to thrombosis: blood stasis, vessel wall injury and blood composition (hypercoagulability); this became known as Virchow's Triad.[1] Our understanding of coagulation, bleeding and the pathophysiology of disease caused by thrombosis has continued to expand. With this expansion of knowledge, the recognition of treatment and prophylaxis has also grown. The Food and Drug Administration (FDA) initially approved heparin sodium for the treatment and prevention of postoperative thrombosis and embolism in 1939.[2]In the early 1920s, the anticoagulant 3,3'-methylenebis(4-hydroxycoumarin) was identified in sweet clover as a cause of fatal hemorrhaging when it was fed to cattle.Once discovered, warfarin was synthesized and used as a rodenticide before being approved for human use.[3]Warfarin, whose name is derived from WARF (Wisconsin Alumni Research Foundation) and *–arin*, was the first oral anticoagulant approved in 1954. It exerts its activity by blocking the regeneration of vitamin K(1) epoxide, therefore inhibiting the generation of vitamin K-dependent clotting factors II, VII, IX and X and the anticoagulant proteins C and S. Although the anticoagulant effect is dominant, procoagulant effects may occur initially due to the long half-life of prothrombin (factor II).[4,5]

Warfarin is an effective agent for the treatment and primary and secondary prophylaxis of thromboembolism due to conditions such as venous thromboembolism (VTE) and prevention of stroke in patients with atrial fibrillation (AF). It is estimated that the prevalence of AF in the United States will increase from 5.2 million cases in 2010 to 12.1 million cases in 2030.[6]Although not all patients with AF will require anticoagulation for stroke prevention, it is important to note that the prevalence of cardiovascular disease (CVD) will increase from 36.9% to 40.5% of the population in the United States between 2010 and 2030.[7] The markers of CVD are hypertension, coronary heart disease (CHD), heart failure (HF) and stroke. These markers are among the criteria used to determine the need for anticoagulation in AF patients ($CHADS_2$ and $CHADS_2VASC$).[8]As the prevalence of AF increases, so may the percentage of patients requiring anticoagulation.Warfarin, a racemic mixture of two isomers, the R and S enantiomers, requires close monitoring and frequent dosage adjustments to maintain efficacy.Both efficacy and safety (risk of bleeding)are monitored using the International Normalized Ratio (INR), which utilizes the patients' prothrombin time (PT) and is

standardized using an international sensitivity index (ISI).[5] Fluctuations in INR can occur for a multitude of reasons. The metabolism of warfarin in the liver is affected by medications that inhibit or induce cytochrome P450 (CYP) 2C9 (S enantiomer which is 2.7-3.8x more potent) and CYP1A2 and CYP3A4 (R enantiomer). The list of medications that affect the anticoagulation of warfarin is extensive and has been extensively studied.[9]In addition to FDA-approved medications, there are a multitude of interactions documented with herbal and alternative therapies, most of which increase the risk of bleeding.[10]Other factors that influence INR include genetic factors, vitamin K containing food and beverages, social history (smoking and alcohol intake), age, physical activity and concomitant disease states.[5]

It is these complexities coupled with the narrow therapeutic window of warfarin, typically with a goal INR of 2.0 – 3.0 or 2.5 – 3.5, whichnecessitate close and regular monitoring. Research suggests that the optimal time in therapeutic range (TTR) is greater than 70%; however, reviews have indicated that most patients managed on warfarin have a TTRranging from 50-75%.[5,11]Pharmacists are trained to monitor for medication related adverse events, drug-drug and drug-food interactions. Utilizing pharmacists specially trained in anticoagulation as physician extenders to work in anticoagulation management services (AMS) and warfarin clinics both in inpatient and outpatient settings have demonstrated improved TTR, lower time to achieve a therapeutic INR value, reduced thromboembolic events and increased patient and physician satisfaction.[12-15]The primary objective of this study was to compare the TTR of patients managed by pharmacists compared to those managed by physicians.

II. METHODS

Setting

The AMS clinic is part of Internal Medicine Faculty Associates (IMFA), a primary care ambulatory clinic that services patients in northern New Jersey and is part of the Atlantic Health System. The clinic is staffed by clinical pharmacists, pharmacy and medical residents and physicians. Clinical pharmacists and physicians have a collaborative practice agreement to manage warfarin initiation and monitoring based on the needs of the patients. The complexity of the patient, labiality of the patient's INR and the patient's schedule are factors used to determine which clinician(s) will see the patient.Every patient that is seen by a pharmacist has a specific 15 minute visit set up for warfarin management. At the warfarin visit, these patients have their INR tested using a point-of-care device. After the patients' INR is recorded in the electronic medical record (EMR), the patient is seen by a clinical pharmacist. The pharmacist documents a standard note in the EMR to help maintain continuity of care (Appendix A). Three important factors relating to warfarin monitoring are reviewed with each patient: medication changes since the previous visit, dietary changes since the previous visit and any signs or symptoms of bleeding. Patients are educated regarding vitamin K-containing foods and the importance of maintaining a consistent diet to minimize INR fluctuations. Also, any upcoming medical or surgical procedures are discussed to determine if warfarin will need to be held and if the patient will require parenteral anticoagulation during the pre-operative and post-operative periods. If the INR is out of range, the patient may either be asked to return the following week for a repeat INR check or the warfarin dose may be adjusted based on a pre-determined titration protocol (Appendix B). Any possible causes of INR fluctuation will be identified and rectified as necessary. The patient will then be given a follow-up INR date. Patients that are newly initiated on warfarin or have INR fluctuations are asked to return more frequently than those who have a stable INR with no changes in their medical history.

Patient Selection

Following review by the Morristown Medical Center institutionalreview board (IRB), a list of all patients who were prescribed warfarin between January 1, 2012 and December 31, 2014 at IMFA was generated using the EMR. Patients were included in the study if they received warfarin with at least two consecutive INR readings during the study period and were managed at IMFA.

Patients were divided into a pharmacist-managed arm and a usual care arm. Patients were included in the pharmacist-managed arm if $\geq$ 50% of their anticoagulation visits during the study period were with a clinical pharmacist. All other patients fell into the usual care arm.

Data Collection

For all patients included in the study, the EMR was reviewed to collect demographic information and relevant clinical information. Demographic information reviewed included age, gender, and comorbidities that could increase the risk of stroke (e.g. hypertension, history of cerebrovascular accident (CVA), history of deep vein thrombosis (DVT) or pulmonary embolism (PE), cancer or diabetes). Indications for warfarin included stroke prevention due to AF, mechanical heart valve, DVT, PE, CVA orthrombophilic condition (e.g. factor V Leiden deficiency, prothrombin gene mutation, antithrombin III deficiency or protein C and protein S deficiency).

INR goals for each patient were recorded based on the patient EMR. Goal ranges were documented as 2.0 – 3.0 or 2.5 –3.5. All INR results documented during the study period were extracted for each patient. Time between INR readings was recorded to calculate the TTR. However, for patients who were newly initiated on warfarin therapy and seen at the AMS clinic for the first time, the first INR reading was excluded from the study.

Endpoints

The primary endpoint of this study was TTR, calculated as the number of days each patient's INR was within the therapeutic range divided by the total number of days on warfarin therapy.[16]

The secondary endpoints included the number of INR tests per patient year, percent of patients who had at least one INR reading > 4 during the study period, percent of patients who received dietary education, had warfarin held for any time period due to planned surgery, were initiated on parenteral therapy due to surgery or subtherapeutic INR, were referred to the hospital or who had a major drug interaction as documented in the visit note.

Statistical Analysis

Multiple tests were run to analyze the data. First descriptive statistics, counts and percentages were acquired. Chi-square analysis was then preformed on the categorical variables to test for an association between groups and the variables. P-values of less than 0.05 indicate statistical significance. Mann-Whitney test was then utilized to compare the continuous data.

III. RESULTS

A total of 136 patients were identified as having received warfarin during the study period. Fourteen patients were excluded from the study because they did not have two consecutive INR readings at AMS clinic. Of the remaining 122 patients, 53 fell into the pharmacist-managed arm while 69 fell into the usual care arm. Baseline characteristics are listed in Table 1. The average age of patients in both groups was 56.9 years. Most patients were receiving warfarin for either atrial fibrillation or a DVT but there were no statistically significant differences in anticoagulation indication or comorbidities between the two groups. Most patients had an INR goal of 2.0 – 3.0. Overall, there were more patients in the usual care arm who had INR goals of 2.0 – 3.0 or 2.5 – 3.5 ($p = 0.031$).

Results are listed in Table 2. The patients in the pharmacist-managed arm achieved a higher TTR compared to the usual care arm (66% vs. 56.6%, $p = 0.028$). The pharmacist-managed arm had a higher number of INR tests per patient year (19.59 vs. 15.04, $p = 0.280$). There was no significant difference in patients who developed at least one INR > 4 during the study period (15 vs. 31, $p = 0.06$) or the number of patients who were urgently referred to the hospital (2 vs. 3, $p = 0.651$) between the two arms. A significantly higher proportion of patients received dietary education from a pharmacist compared to a physician ($p < 0.001$), as documented in the EMR. There were also more patients in the pharmacist-managed arm who had a documented major drug-drug interaction while receiving warfarin during the study period (10 vs. 3, $p = 0.044$).

IV. DISCUSSION

Patients who are managed in the internal medicine clinic demonstrate high level anticoagulation therapy management with a TTR over 55%.However, patients in the pharmacist-managed arm had a significantly higher TTR compared to the usual care arm (66% vs. 56.6%, $p = 0.028$).TTR is important due to the interactions with diet, other drugs, and comorbidities that may alter anticoagulation control. A multitude of studies have correlated higher TTR with lower morbidity and lower healthcare costs.[17-19]

In addition, our findings demonstrate that patients under the care of the pharmacists received significantly more dietary education. Dietary education is important in patients taking warfarin because of its interaction with vitamin K-containing foods. Patients stabilized on warfarin can have fluctuationsin their INR if a consistent diet is not maintained. Patients were also seen more often and had their INRs checked more frequently in the pharmacist-managed arm. Frequent monitoring has been shown to improve anticoagulation control and decrease unnecessary adverse events. Referrals to seek emergency care and need to hold doses due to surgery were similar in both groups.As with all studies, our study also had its limitations. One significant aspect of warfarin therapy that affects INR is compliance. Patients that are non-compliant with refilling warfarin or remembering to take it on a daily basis can have fluctuations in their INR. Unfortunately, we were not able to ascertain the compliance of our study patients, which could impact the TTR.Overall, patients experienced enhanced anticoagulation control when their warfarin was managed by clinical pharmacists working in a collaborative practice setting with internal medicine physicians without increased risk for adverse events. Based on the findings, utilizingpharmacists as part of anticoagulation management services can be beneficial to the overall care of the patient.

Table 1: Baseline Characteristics

	Pharmacist-Managed Arm (n = 53)	Usual Care Arm (n = 69)	P Value[a]
Gender			
Male Female	31 22	37 33	0.592
Mean Age (years)	56.9	56.9	0.944
Anticoagulation Indication			
Atrial fibrillation	23	25	0.422
Mechanical heart valve	3	9	0.175
DVT	20	30	0.523
PE	10	14	0.845
CVA	4	7	0.619
Thrombophilia	4	5	0.950
Other	5	6	0.888
Comorbidities			
Hypertension	31	43	0.668
Previous CVA	2	5	0.414
Previous DVT/PE	4	13	0.075
Cancer	6	6	0.629
Diabetes	17	34	0.056
INR Goals			
2.0 – 3.0	51	58	0.031
2.5 – 3.5	2	11	0.031

[a]A p value of < 0.05 indicates statistical significance

Table 2: Results

	Pharmacist-Managed Arm (n = 53)	Usual Care Arm (n = 69)	P Value [a]
TTR	66%	56.6%	0.028
INR > 4	15	31	0.06
Total Number of INR Tests	1383	1629	0.547
Total Patient Years	70.6	108.3	0.280
INR Tests Per Patient Year	19.59	15.04	0.0113
Dietary Education	104/122	20/122	< 0.001
Medication Held for Surgery	12	11	0.827
Parenteral Agent Initiated	5	9	0.270
Referred to Hospital	2	3	0.651
Medication Interaction	10	3	0.044

[a]A p value of < 0.05 indicates statistical significance

Appendix A: Clinical Pharmacist Note

General: _____

_____

Indication for Anticoagulation: _____
Goal INR: _____
Warfarin regimen and total weekly dose: _____
Tablet size: _____

Today's INR: _____
Previous visit INR: _____
Last hemoglobin/hematocrit: _____
Medication changes since last visit: _____
Dietary changes since last visit: _____
Signs/symptoms of bleeding: _____

Regimen changes (if any): _____
Follow-up INR date: _____
Medication refills (if any): _____
Follow up complete blood count date: _____
Considerations for next visit: _____

Appendix B: Dose Adjustment Based on INR

Warfarin Dose Adjustment Recommendations for INR Goal 2 – 3	
1.0 – 1.4	Increase weekly dose by 10-20%
1.5 – 1.9	Increase weekly dose by 5-10%
2.0 – 3.0	No dose adjustment necessary
3.1 – 3.4	Decrease weekly dose by 5-10%
3.5 – 3.9	Decrease weekly dose by 10-15%
4.0 – 5.0	Hold dose x 1. Decrease weekly dose by 15-20%
Greater than 5	Hold dose.

Warfarin Dose Adjustment Recommendations for INR Goal 2.5 – 3.5	
1.0 – 1.4	Increase weekly dose by 20-30%
1.5 – 1.8	Increase weekly dose by 15%
1.9 – 2.4	Increase weekly dose by 10%
2.5 – 3.5	No dose adjustment necessary
3.6 – 4.5	Decrease weekly dose by 5-10%
4.5 – 5.0	Hold dose x 1. Decrease weekly dose by 10-20%
Greater than 5	Hold dose.

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